JACC: ADVANCES VOL. 1, NO. 4, 2022

STATE-OF-THE-ART REVIEW

CRITICAL CARE CARDIOLOGY

Advances in the Staging and Phenotyping of Cardiogenic Shock

Part 1 of 2

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ABSTRACT

Cardiogenic shock (CS) is a heterogeneous syndrome reflecting a broad spectrum of shock severity, diverse etiologies, variable cardiac function, different hemodynamic trajectories, and concomitant organ dysfunction. These factors influence the clinical presentation, management, response to therapy, and outcomes of CS patients, necessitating a tailored approach to care. To better understand the variability inherent to CS populations, recent algorithms for staging the severity of CS have been described and validated. This paper is part 1 of a 2-part state-of-the-art review. In this first article, we consider the context for clinical staging and stratification in CS with a focus on established severity staging systems for CS and their use for risk stratification and clinical care. We describe the use of staging for predicting outcomes in populations with or at risk for CS, including risk modifiers that provide more nuanced risk stratification, and highlight how these approaches may allow individualized care. (JACC Adv 2022;1:100120) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

DEFINITION AND EPIDEMIOLOGY OF CARDIOGENIC SHOCK

Cardiogenic shock (CS) is a complex clinical syndrome characterized by the clinical triad of: 1) tissue and organ hypoperfusion; 2) ineffective cardiac output (CO); and 3) normal or elevated cardiac filling pressures (congestion).[1] Definitions of CS used to define eligibility for research studies vary, but conserved elements include sustained hypotension or the requirement for vasoactive agents to maintain an adequate blood pressure; clinical or biochemical evidence of end-organ hypoperfusion (such as altered mental status, cool or mottled extremities, oliguria, ischemic liver or kidney injury, or lactic acidosis); and low CO despite normal or elevated ventricular filling

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received April 3, 2022; revised manuscript received June 30, 2022, accepted August 11, 2022.

ISSN 2772-963X https://doi.org/10.1016/j.jacadv.2022.100120

ABBREVIATIONS AND ACRONYMS

AMI = acute myocardial infarction

CA = cardiac arrest

CICU = cardiac intensive care unit

CO = cardiac output

CS = cardiogenic shock

DPP-3 = dipeptidyl peptidase-3

HF = heart failure

HTE = heterogeneity of treatment effect

IABP = intra-aortic balloon pump

MCS = mechanical circulatory support

PCI = percutaneous coronary intervention

RCT = randomized controlled trial

SCAI = Society for Cardiovascular Angiography and Intervention

pressures based on clinical assessment or invasive hemodynamic measurements.[1-6] Although sustained hypotension is typically required to define CS for clinical trial enrollment, an increasingly recognized subgroup of patients with CS have isolated hypoperfusion without hypotension, and the concept of "normotensive CS" has been proposed.[7]

Despite advancements in the management of CS, including early percutaneous coronary intervention (PCI) for patients with CS due to acute myocardial infarction (AMI), in-hospital mortality remains unacceptably high, with estimates ranging between 30% and 50% in contemporary registries and clinical trials.[4-6,8-13] To overcome the limitations of the vasopressors and inotropes that have been traditionally used to provide hemodynamic support in CS, a variety of temporary mechanical circulatory support (MCS) devices have been developed to improve hemodynamics in CS.[14] Randomized controlled trials (RCTs) to date have failed to demonstrate improved survival with these MCS devices in spite of their favorable hemodynamic effects, underscoring the complexity of the CS syndrome and our need for improved mechanistic understanding of the disease.[5,8,15,16] Indeed, no novel therapies or treatment strategies have demonstrated an improvement in survival in an RCT in patients with CS in the past 2 decades, and this may in part relate to inadequately accounting for patient heterogeneity in their study design.[8,17] There is a pressing need to evolve from a hemodynamic model of CS treatment to a disease-modifying model that encompasses the nuances and complexity of CS as a multisystemic clinical syndrome.[18,19]

In this 2-part state-of-the-art review series, we will critically examine the evidence that CS is a heterogeneous condition with highly variable disease severity, outcomes, clinical manifestations, and pathobiology and discuss the implications of this multidimensional heterogeneity for improving the care of patients with CS. In part 1, we will discuss clinical staging based on illness severity and its implications for risk stratification and introduce the concept of subphenotyping as a way to understand heterogeneous populations. In part 2, we will review innovative methodology for subphenotyping and applications of subphenotyping in critical illnesses including CS, with a focus on applying staging and subphenotyping for more reliable and personalized evidence evaluation.[20]

HIGHLIGHTS

- Cardiogenic shock manifests heterogenous severity and clinical phenotypes.
- The SCAI Shock Classification stratifies shock severity and predicts mortality.
- Risk modifiers can improve mortality risk stratification beyond shock severity.
- Phenotypes can be integrated into standard measures of cardiogenic shock severity.
- Subphenotyping can identify specific treatable underlying disease processes.

CLINICAL HETEROGENEITY OF CS. Although CS research has traditionally focused on severe left ventricular dysfunction complicating AMI, recent studies have highlighted the substantial clinical heterogeneity of CS, including its diverse underlying causes, hemodynamic patterns, and clinical risk profiles.[10,12,13,21,22] In tertiary-care cardiac intensive care units (CICUs) in the Critical Care Cardiology Trials Network, only 30% of CS cases were related to AMI, and most of the remaining cases were associated with decompensated chronic heart failure (HF).[10] In a cohort of CS patients treated in German hospitals between 2005 and 2017, an increasing proportion of non-AMI causes of CS were observed over time; a similar trend was observed in patients with CS admitted to the Mayo Clinic CICU from 2007 to 2018.[12,13] This changing epidemiology of CS has motivated a shift toward distinguishing AMI-CS and CS due to decompensated HF (HF-CS) as distinct clinical entities.[22-26] The recognition of HF-CS as a distinct disease entity with important differences from AMI-CS is essential considering that the vast majority of RCTs enrolling CS patients have focused on AMI-CS, and the results may not apply to HF-CS.[8,25] Furthermore, important differences exist within the HF-CS population, including those defined by chronicity of HF (ie, de novo HF vs chronic advanced HF).[25] Patients with chronic advanced HF may have compensatory adaptations that allow them to tolerate a degree of hemodynamic compromise that a patient without preexisting HF might not, resulting in different CS manifestations between these groups.[22,25]

Patterns of blood pressure, vascular tone, and cardiac filling pressures can vary widely in CS

populations and may necessitate divergent management strategies.[1] Vasodilatory CS is an increasingly prevalent subgroup with a hemodynamic profile characterized by concomitant low systemic vascular resistance and reduced CO that appears to have worse outcomes.[1,10,12,27,28] There are multiple secondary pathophysiologic processes that can lead to vasodilatory CS, including concurrent infection or a noninfectious inflammatory response; metabolic derangements such as multiorgan failure and acidosis (sometimes termed hemometabolic CS); vasoplegia after cardiac arrest (CA) or cardiac surgery; vasodilatory medications; or interpatient differences in the immune response to acute insults.[10,12,29-31] Uncertainty remains regarding whether vasodilatory CS is a unique disease state or the final common pathway of prolonged or undertreated CS. Furthermore, a rising frequency of right ventricular involvement in CS has been identified using a variety of echocardiographic and hemodynamic parameters and is associated with worse outcomes compared with CS due to isolated left ventricular failure.[22,32,33] The presence of right ventricular predominant or biventricular CS may limit the utilization of univentricular support strategies with temporary or durable left-sided MCS devices, greatly influencing therapeutic options.[14]

STAGING OF CS SEVERITY

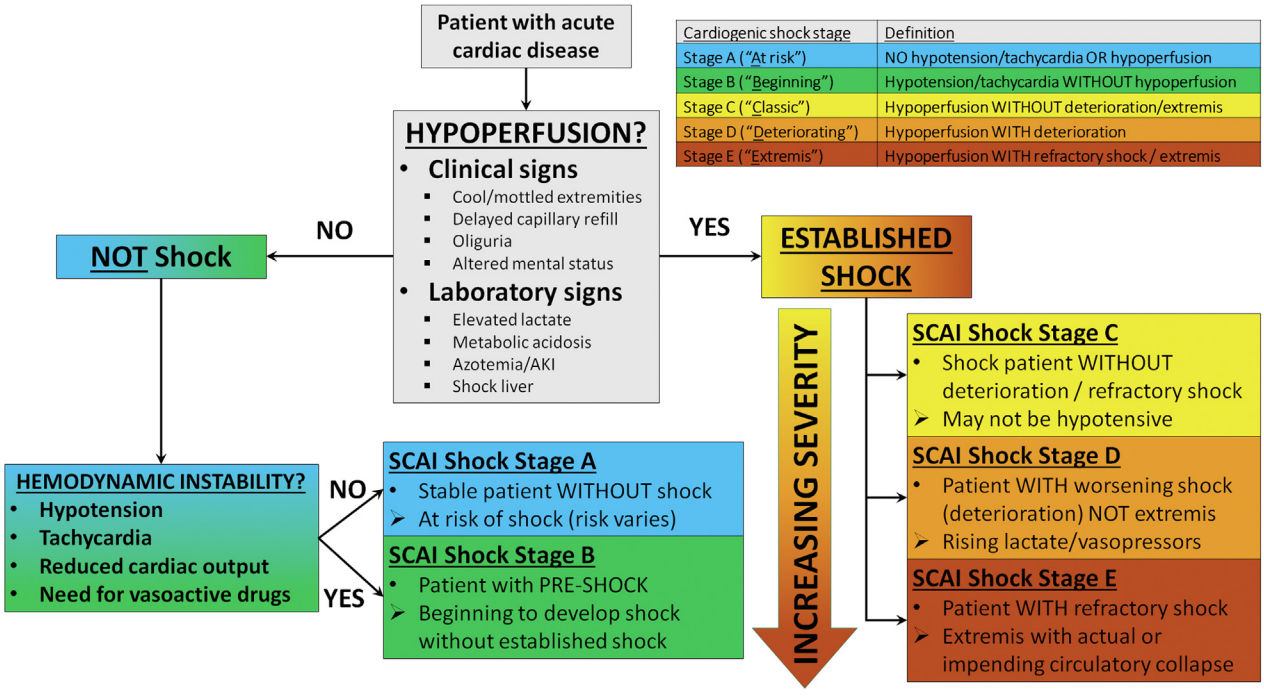
SEVERITY ASSESSMENT IN CS. The severity of hemodynamic compromise is an important determinant of prognosis in patients with CS.[34] The most commonly recognized individual markers of shock severity used to predict mortality in CS have been vasoactive drug requirements and serum lactate, both being nonspecific risk markers that apply equally to patient cohorts without CS.[34-42] Hemodynamic measurements such as mean arterial pressure, CO, and derived indices such as cardiac power output may further quantify CS severity and prognosis.[38,43] Each of these individual variables fails to adequately capture the spectrum of shock severity on its own, but the combination of hemodynamics and other markers of shock severity may improve risk stratification.[38]

The need to establish a unifying system for grading the severity of CS to guide clinical practice compelled development of the Society for Cardiovascular Angiography and Intervention (SCAI) Shock Classification.[44] Patients with acute cardiovascular disease are stratified into 5 SCAI Shock stages of escalating severity, from A ("At risk": patients without shock) to E ("Extremis": patients with refractory shock). Within the context of the SCAI Shock Classification (**Figure 1**), shock is defined as hypoperfusion requiring intervention and encompasses SCAI Shock stages C (established shock), D (worsening shock), and E (refractory shock). Patients with SCAI Shock stage B ("beginning") do not have manifest hypoperfusion and do not meet criteria for established shock, yet they are beginning to develop shock and are considered to have preshock.[7,44,45] The severity of CS exists on a continuous spectrum even though the SCAI Shock Classification defines discrete stages, and within each SCAI Shock stage, there will be patients with varying degrees of hemodynamic compromise. Gradations of hypotension and hypoperfusion have been associated with prognosis, with hypoperfusion being the more important predictor of mortality.[7] This has important implications for distinguishing preshock (SCAI Shock stage B) from early shock (SCAI Shock stage C).[45]

The SCAI Shock Classification was intended to serve a variety of goals including streamlining communication of CS severity, facilitating timely decision-making regarding triage and treatment, and providing a framework for prospective stratification of patients by shock severity in clinical research.[44] The SCAI Shock Classification has also proven to be a robust predictor of mortality and a useful guide for clinical practice.[19,45] Although the SCAI Shock Classification was developed for cardiac patients, it may be equally applicable to other causes of shock such as sepsis, allowing broader utilization and dissemination in patient care.[28]

VALIDATION OF THE SCAI SHOCK CLASSIFICATION. The SCAI Shock Classification has demonstrated applicability in both clinical and research settings, providing a universal language to communicate the severity of CS. Since the publication of the SCAI Shock Classification in 2019, numerous analyses have demonstrated its ability to provide mortality risk stratification across diverse populations, as recently reviewed in the 2022 SCAI Shock Classification update.[45] Each additional SCAI Shock stage confers an incrementally higher risk of short-term mortality in populations of CS patients, CICU patients, patients with CA, and even patients with sepsis.[21,22,28,46-60] The SCAI Shock Classification provides post-discharge mortality risk stratification among CICU patients who survive hospitalization.[61] Each publication has utilized a subtly different research definition of the SCAI Shock Classification, but despite these modifications, its ability to perform risk stratification has been preserved (**Figure 2**). Prospective application of the SCAI Shock Classification is simple in clinical practice and appears to retain strong prognostic value without using a rigorously applied definition.[47] The

FIGURE 1 Determination of SCAI Shock Stage Using the SCAI Shock Classification



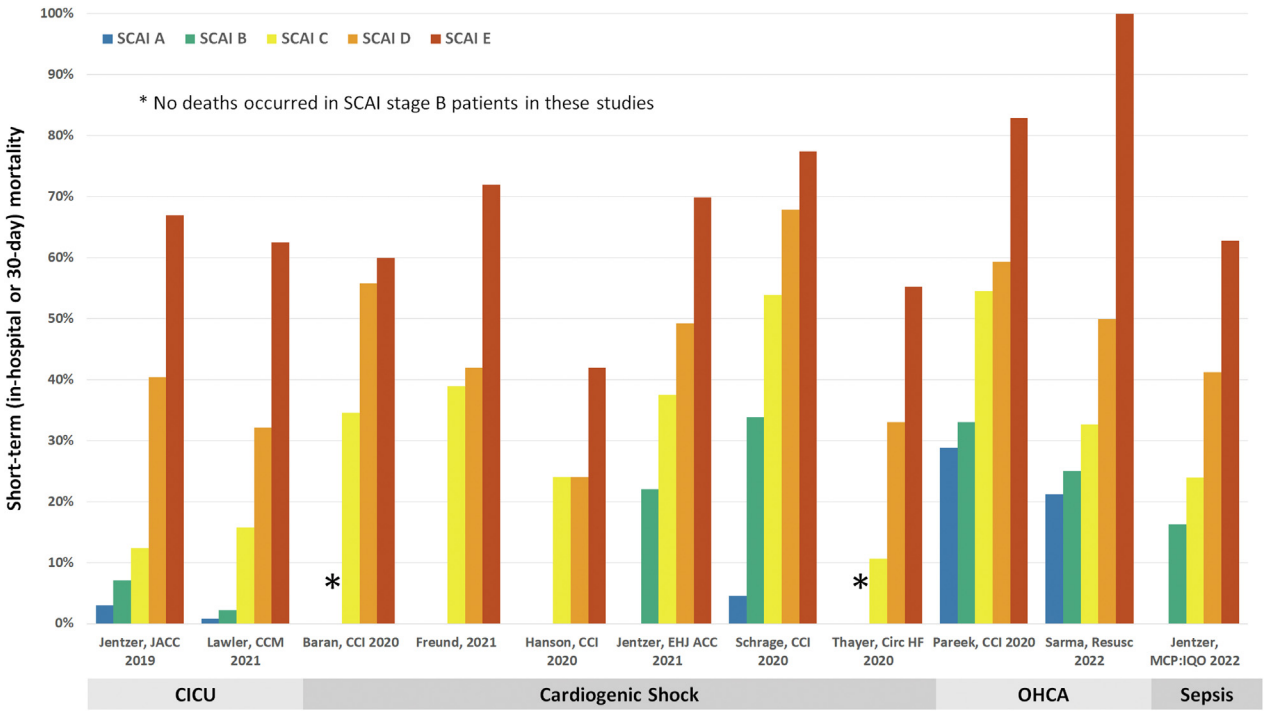
Patients without hypoperfusion **(left)** do not meet criteria for established shock and are grouped into SCAI Shock stage A vs B based on the presence of hemodynamic instability. Patients with hypoperfusion **(right)** are classified as shock and further graded into SCAI Shock stages C, D, or E based on the severity. It is essential to recognize that a spectrum of CS severity exists within each SCAI Shock stage. AKI = acute kidney injury; SCAI = Society for Cardiovascular Angiography and Intervention.

SCAI Shock Classification is inherently dynamic, and a rising or persistently elevated SCAI Shock stage portends worse outcomes; the SCAI Shock stage trajectory and presumably the duration of time spent in higher SCAI Shock stages are additional prognostic variables.[47,49]

RISK MODIFIERS AND MORTALITY. Analogous to the spectrum of shock severity that exists within each SCAI Shock stage, there likewise exists variable mortality risk at each level of shock severity. A crucial distinction must be made between shock severity and mortality risk in patients with CS, as a broad range of risk and residual heterogeneity may exist within each SCAI Shock stage.[34,45,62] While studies have consistently identified various measures of shock severity as important predictors of outcomes, there are numerous risk factors for mortality in CS that are not directly related to shock severity.[9,41,59,62,63] Prognostic factors that provide additional mortality risk stratification beyond the SCAI Shock stage are referred to in the SCAI Shock Classification framework as "risk modifiers" (**Table 1**).[22,30-33,42,44,46-50,52,53,57,64-69] Most established and proposed risk modifiers are nonmodifiable risk factors for death (eg, older age) which identify high-risk patients at elevated risk of adverse outcomes across the spectrum of shock severity (**Figure 3A**).[53,64,68] Notably, patients in a lower SCAI Shock stage with high-risk features may have observed mortality risk similar to or exceeding that of patients in a higher SCAI Shock stage with low-risk features.[65,67] Composite risk scores designed to predict mortality in CS populations will necessarily correlate with shock severity but can provide complementary information by identifying high-risk subgroups in each SCAI Shock stage while the SCAI Shock Classification can provide additional mortality risk stratification across the spectrum of risk as defined using a risk score.[59,60,62]

Although the prevalence of most risk modifiers varies with shock severity, by definition, they retain an independent prognostic value and improve risk stratification across the SCAI Shock Classification.[45] Some proposed risk modifiers (eg, lactate levels, vasopressor doses) directly reflect the severity of CS and may help to refine the SCAI Shock Classification by identifying patients with higher vs lower shock severity (and therefore mortality risk) in each SCAI Shock stage.[42] Risk modifiers that reflect underlying

FIGURE 2 **Observed Short-Term Mortality as a Function of SCAI Shock Stage in Published Validation Cohorts**



Each study has shown a stepwise increase in mortality with each higher SCAI Shock stage, including a variety of different populations. Adapted from Naidu et al.[45]
CICU = cardiac intensive care unit; OHCA = out-of-hospital cardiac arrest; SCAI = Society for Cardiovascular Angiography and Intervention.

cardiac function and hemodynamics are interrelated with, but distinct from, shock severity per se and may help to characterize the phenotype of CS.[20,45] For example, invasive hemodynamic measurements and echocardiographic findings have shown additive prognostic value beyond the SCAI Shock Classification itself.[22,32,33,48,67] Large differences in systemic hemodynamic measurements have not been observed across the SCAI Shock stages in CS patients, suggesting that the integrity of compensatory mechanisms that preserve perfusion is an important determinant of shock severity.[22,47,48] The association between some risk modifiers and outcomes can vary according to the SCAI Shock stage, highlighting the potential interaction between shock severity and additional prognostic factors.[53,64,68]

The presence of concomitant CA complicating CS can aggravate hemodynamic compromise, multiorgan failure, and metabolic derangements via multiple pathways, driving important clinical differences among CS patients that influence prognosis and response to treatment.[17,50,70] CA becomes more common as the SCAI Shock stage increases, yet patients with CA are more likely to die in each SCAI Shock stage

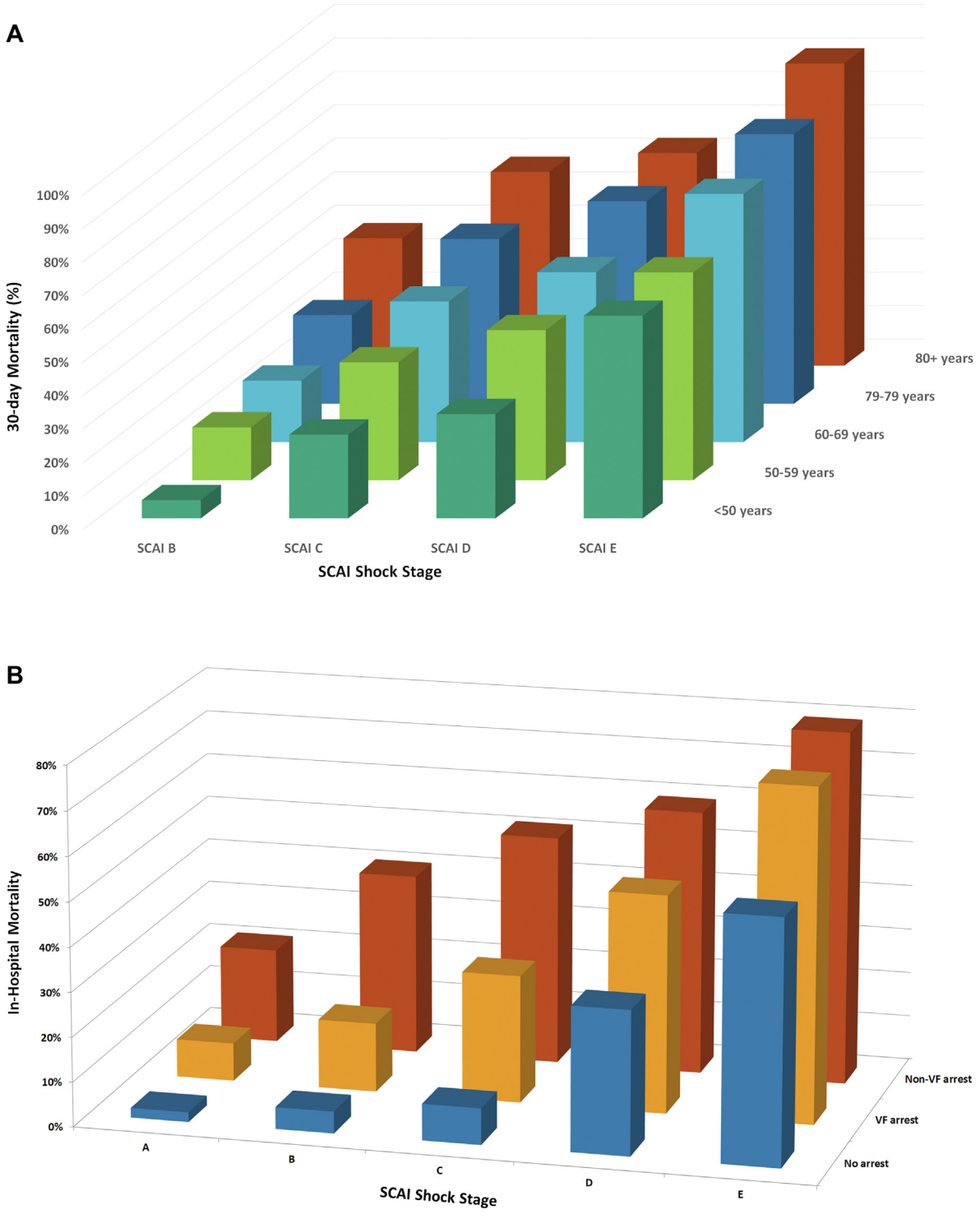
TABLE 1 **Established and Proposed Risk Modifiers That May Provide Mortality Risk Stratification on Top of the SCAI Shock Classification**

Established Risk Modifiers	Proposed Risk Modifiers
Age	Vasopressor/inotrope doses
Cardiac arrest	Unshockable vs shockable rhythm
Right ventricular failure	Presence of coma/anoxic brain injury
Elevated RAP, echocardiographic RV dysfunction	
Systemic hemodynamics	Noncardiac organ failure
Low MAP, high HR, low SVI	
Systemic inflammation	Acute kidney injury
SIRS, neutrophil-to-lymphocyte ratio	
Hemometabolic shock	Echocardiography
Metabolic (lactic) acidosis	Low LVEF, high mitral E/e' ratio
Worsening shock	Invasive procedures
Rising SCAI shock stage, late deterioration	Use of PAC or IABP

Established risk modifiers have been demonstrated in at least 2 published analyses from different cohorts. Proposed risk modifiers have been demonstrated in either a single published analysis or multiple analyses from the same cohort.

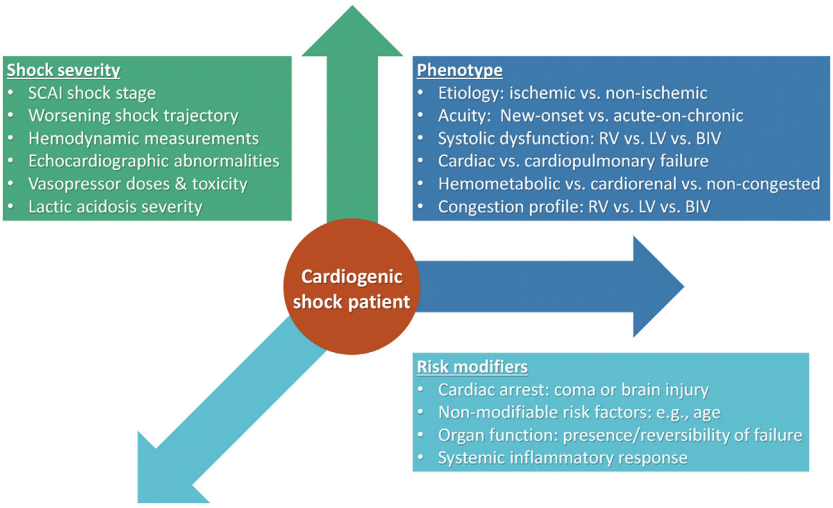
HR = heart rate; IABP = intra-aortic balloon pump; LVEF = left ventricular ejection fraction; MAP = mean arterial pressure; PAC = pulmonary artery catheter; RAP = right atrial pressure; RV = right ventricular; SCAI = Society for Cardiovascular Angiography and Intervention; SIRS = systemic inflammatory response syndrome; SVI = stroke volume index.

FIGURE 3 Observed Short-Term Mortality in Each SCAI Shock Stage



Mortality according to age **(A)** and the presence and type of cardiac arrest **(B)**, highlighting the 2 best-characterized risk modifiers for the SCAI Shock Classification. Risk modifiers influence the observed mortality risk independent from the severity of CS. Adapted From Jentzer et al.[50,53] SCAI = Society for Cardiovascular Angiography and Intervention; VF = ventricular fibrillation.

FIGURE 4 3-Axis Model for Conceptualization of Risk Stratification and Clinical Decision-Making in Patients With CS



The severity of CS involves multiple components, yet only represents one important aspect of CS evaluation. The phenotype of CS and the presence of risk modifiers influence mortality risk as well as candidacy for certain therapies. Adapted from Naidu et al.[45] LV = left ventricular; RV = right ventricular; SCAI = Society for Cardiovascular Angiography and Intervention.

(Figure 3B); as a result, CA was the first recognized risk modifier (designated as the "A" modifier) within the SCAI Shock Classification.[44-46,50] CA often causes anoxic brain injury, which is a critical determinant of outcomes that may not be modifiable by cardiovascular therapies.[17] Not all patients with CA have the same risk of anoxic brain injury and adverse outcomes, and the "A" modifier applies primarily to those who remain comatose after resuscitation.[17,45,50] Clinical variables such as the arrest rhythm and duration of resuscitation can refine mortality risk stratification among comatose patients with CA.[17,50,60,70]

INTEGRATED RISK STRATIFICATION IN CS. A 3-axis model for conceptualizing CS patients in terms of risk stratification and clinical decision-making has been proposed, with the principal components that describe an individual's condition by defining their position within a theoretical 3-dimensional space and a greater distance from the origin implying higher risk (Figure 4).[45] This model separates prognostic variables into: 1) those directly related to shock severity; 2) those related to clinical phenotypes; and 3) risk modifiers, in order to better understand their separate contributions to outcome and to guide management in CS patients. This conceptual model is designed as a heuristic for integrating the multitude of clinical variables describing each patient's condition, recognizing that available data are inadequate to translate this into a specific prognosis or treatment plan. In the context of this model, we propose that at a given level of shock severity, the desired temporary or durable MCS platform will be influenced by factors such as the pattern of ventricular dysfunction/congestion and patient characteristics that will ultimately guide candidacy.[14] In this paradigm, interventions to improve hemodynamics (such as temporary MCS) are less likely to be beneficial in patients who are at elevated risk of death due to a high burden of nonmodifiable risk factors despite low shock severity.[14,34] This phenomenon was demonstrated in the IMPRESS (IMPella versus IABP Reduces mortality in STEMI patients treated with primary PCI in Severe cardiogenic SHOCK) trial comparing the intra-aortic balloon pump (IABP) vs a percutaneous microaxial continuous flow pump in an AMI-CS cohort including predominantly patients with preceding CA, in which anoxic brain injury exceeded refractory CS as a cause of death.[16] This concept is essential when utilizing mortality risk stratification scores for patients with CS, as patients with high risk score values may not necessarily have severe shock warranting an escalation of hemodynamic support.[9,41,59,62,63]

FUTURE DIRECTIONS FOR THE SCAI SHOCK CLASSIFICATION. Prospective studies have demonstrated that clinician assignment of the SCAI shock stage can be performed effectively during the routine course of care for CS patients.[47] Considering the many successful approaches to applying the SCAI Shock Classification in published studies, each

TABLE 2 Remaining Clinical and Research Questions Regarding the SCAI Shock Classification

Category	Questions
Definitions of CS itself	Is relative or absolute hypotension required to define the presence of CS?
	How should normotensive CS be defined clinically?
	In the absence of hypotension, should multiple markers of hypoperfusion or certain hemodynamic criteria be required to define normotensive CS?
	Should patients who require vasopressor or inotropes in the absence of established hypoperfusion be defined as CS?
Refining the SCAI Shock Classification	Which variables are most important to incorporate into defining each SCAI Shock stage to create a parsimonious classification?
	Which measures of hypoperfusion are necessary or sufficient to define shock?
	How should a patient be graded if different hypoperfusion markers disagree?
	What are the ideal cutoffs for each of the proposed hemodynamic and laboratory variables used to define each SCAI Shock stage?
	What duration and intensity of intervention is required prior to determining that a patient is deteriorating (SCAI Shock stage D)?
Applying the SCAI Shock Classification across subgroups	Should the diagnostic criteria for shock (and the SCAI Shock stage definitions) differ for AMI-CS vs HF-CS?
	How should shock after CA be defined, considering that global hypoperfusion from resuscitation is expected to cause an elevated lactate?
Definition of the "A" modifier	What degree of impairment in mental status after CA is necessary to justify the "A" modifier?
	How should CA patients with CPR-in-progress (including extracorporeal CPR) be classified?
Clinical decision-making	How can the SCAI Shock Classification be most efficiently integrated into clinical workflow?
	How should the SCAI Shock Classification be used to guide treatment decisions?
	How can established risk modifiers best be integrated into the SCAI Shock Classification for outcome prediction?
	How should the presence of risk modifiers be used for decision-making in the context of the SCAI Shock Classification?
	How can the 3-axis model integrating the SCAI Shock Classification be operationalized for patient care?

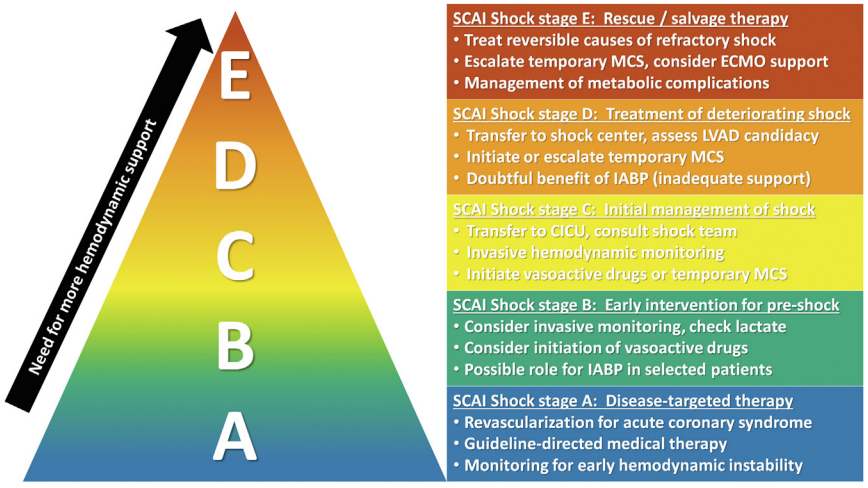
AMI = acute myocardial infarction; CA = cardiac arrest; CPR = cardiopulmonary resuscitation; CS = cardiogenic shock; HF = heart failure; SCAI = Society for Cardiovascular Angiography and Intervention.

health system can devise their own flexible approach to using the SCAI Shock Classification, facilitating application by providers with different expertise. For example, the SCAI Shock Classification might be simplified for use in the prehospital and early emergency department settings, where clinical information is limited and patients are undifferentiated. Such an approach might enable early recognition and rapid triage so that patients with manifest CS could be triaged to a shock center, analogous to the ST-segment elevation myocardial infarction processes of care. Questions remain regarding the optimal application of the SCAI Shock Classification in clinical practice and research, particularly considering the numerous variables that can be incorporated to define each SCAI Shock stage (Table 2).

It will be important to establish how best to apply the SCAI Shock Classification in the context of clinical trials in CS patients, recognizing that the SCAI Shock stage can change quickly after interventions such as PCI or initiation of MCS and that serial assessment of SCAI Shock stage should ideally be performed. We believe that the SCAI Shock Classification and "A" modifier should be prospectively assessed at the time of screening/enrollment. Prospective studies may consider a hybrid approach which uses standardized criteria to streamline SCAI Shock stage assessment by clinicians while allowing the flexibility of individuals' clinical judgement. Contemporary electronic health record systems present a unique opportunity to leverage the SCAI Shock Classification for real-time staging of shock severity in hospitalized patients, which can facilitate early recognition of new or impending CS, easily identify patients for study enrollment, and enable timely intervention using standardized order sets for each SCAI Shock stage.

THE USE OF SHOCK SEVERITY STAGING TO GUIDE PATIENT CARE. Treating patients based on broad clinical syndromes such as CS often results in a "one-size-fits-all" approach that fails to account for individual treatment responsiveness between patients (ie, heterogeneity of treatment effect, as discussed in more detail in part 2[20]).[71,72] Broadly, a staging-based management approach matches the type and intensity of treatment to the severity and prognosis of the disease. An example relates to the use of complete revascularization vs culprit-only PCI in AMI, whereby complete revascularization was beneficial compared with culprit-only revascularization in stable patients with ST-segment elevation myocardial infarction who did not have CS but may have been harmful in patients with established AMI-CS.[6,73] A similar pattern was seen with percutaneous temporary MCS devices, where RCTs in patients with AMI-CS showed no benefit while those in stable patients receiving PCI may have showed a possible benefit.[5,15,74] If the benefit of a certain intervention only exists in low-severity patients, then a hypothetical RCT enrolling a nonstratified cohort of patients with AMI-CS across the spectrum of CS severity could yield an overall neutral result with underpowered post hoc subgroup analyses despite a meaningful effect in this subgroup.[71] Without being able to retrospectively stratify published RCT populations by SCAI Shock stage, we cannot be certain whether the overall neutral results belie a beneficial effect in patients with higher or lower CS severity.[8]

FIGURE 5 Hypothetical Management Strategy Tailored to the SCAI Shock Stage



While the specifics of such a strategy should be determined by an individual institution based on accepted local practices and resource availability, the conceptual framework could help to provide more consistent care as a function of CS severity. The ideal treatment strategy would account for the CS phenotype, including AMI-CS vs HF-CS and RV vs LV dysfunction. Adapted from Wiley et al.[75] AMI-CS = acute myocardial infarction-cardiogenic shock; CICU = cardiac intensive care unit; ECMO = extracorporeal membrane oxygenator; HF-CS = heart failure-cardiogenic shock; IABP = intra-aortic balloon pump; LV = left ventricular; LVAD = left ventricular assist device; MCS = mechanical circulatory support; RV = right ventricular; SCAI = Society for Cardiovascular Angiography and Intervention.

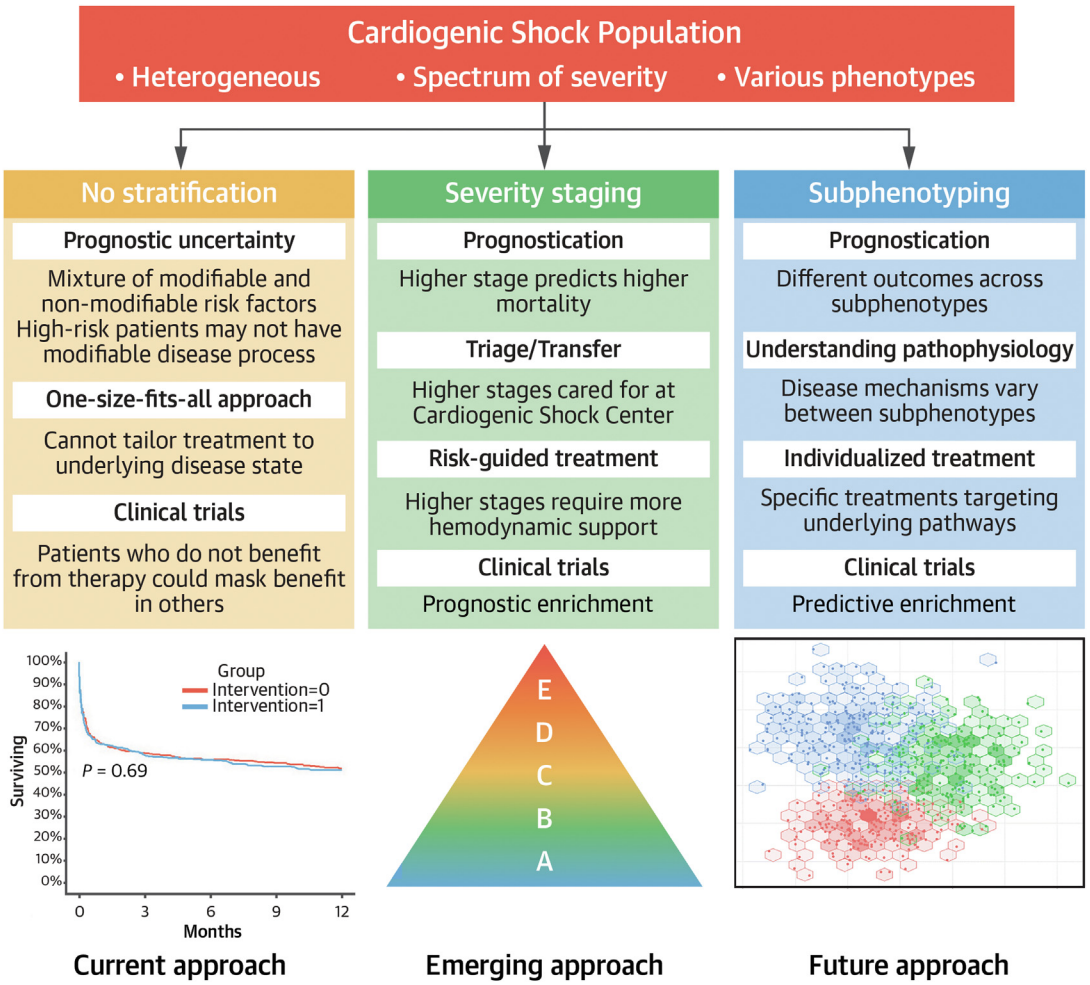
The use of the SCAI Shock Classification to guide temporary MCS device selection has been proposed, based on the premise that more powerful MCS devices are needed in patients with greater degrees of hemodynamic compromise (**Figure 5**) although this approach remains speculative.[75] One retrospective study found that the use of an IABP was associated with lower in-hospital mortality in a mixed cohort of patients with AMI-CS and HF-CS after propensity adjustment, with a suggestion of greater relative benefit in patients in lower SCAI Shock stages; however, this type of study cannot exclude the presence of confounding by indication favoring those who received an IABP.[66]

SUBPHENOTYPING IN CS

RATIONALE FOR SUBPHENOTYPING. While strategies such as grouping patients on the basis of causative etiology, hemodynamic profile, or SCAI Shock stage may provide important risk stratification, subgroups defined by these parameters remain quite heterogeneous.[1,22,25,33,44] Understanding disease heterogeneity as it relates to specific disease mechanisms as well as physiologic and biologic responses may allow individualized treatment (**Central Illustration**). Using more nuanced approaches that provide insight into underlying pathophysiologic mechanisms may allow us to transition from the typical syndromic or risk-based approach to defining CS to a mechanistic approach that embraces the heterogeneity within the CS population. This is the basic rationale for subphenotyping, defined herein as identifying reproducible patterns of biomarkers or other clinical variables that identify specific underlying disease mechanisms.

Various terms have been used to label patient subgroups within a population although these terms do not have precise consensus definitions (**Table 3**).[76,77] For the purposes of this discussion, we will focus on 2 specific subgroup labels: subphenotype, which refers to a subgroup defined by a specific pattern of clinical and/or biomarker features; and treatable trait, which refers to a subphenotype that has an underlying pathophysiologic mechanism that can be targeted by a specific therapy. Unsupervised machine learning clustering/partitioning methods (as discussed extensively in part 2[20] of this review) are increasingly used to identify unrecognized subgroups in populations of patients with cardiac disease or critical illness, including those with CS.[56,57] While not all the subgroups identified using these methods will be true subphenotypes or treatable traits, these methods can provide crucial insights

CENTRAL ILLUSTRATION **Demonstration of Potential Applications of Staging and Subphenotyping in the Clinical Care of Patients With CS and the Limitations of Not Using These Approaches**



Jentzer JC, et al. JACC Adv. 2022;1(4):100120.

The current approach to CS management fails to account for the heterogeneity of the CS population and has resulted in no incremental improvements in survival in published RCTs. An emerging approach would scale the aggressiveness of intervention to the severity of CS based on a staging algorithm such as the SCAI Shock Classification, to ensure that the degree of support matches the degree of hemodynamic compromise. A proposed future approach would individualize care based on the underlying CS subphenotype, matching specific therapies to each patient's pathophysiology.

into heterogeneity beyond traditional statistical approaches.

SUBPHENOTYPING FOR PROGNOSTICATION. Most published studies examining subphenotypes in critically ill patient populations have reported differences in outcomes to validate the distinctions between groups.[56,57] However, subphenotypes can display fundamental differences that are clinically meaningful without resulting in dissimilar outcomes; for example, one subgroup of patients may have higher acute illness severity, and another subgroup may have greater chronic comorbidity burden, yet the subgroups may have similar short-term outcomes.[56] Insofar as a goal of subphenotyping is to gain insight into the underlying pathophysiology with a view toward delivering more personalized treatments, using outcomes as the only metric to validate phenotypes is suboptimal, and clustering methods

TABLE 3 Proposed Definitions of Commonly Used Terminology to Describe Heterogeneity Within a Population

Term	Definition
Phenotype (or phenogroup)	Patient group with a distinct clinical pattern
Subphenotype	Patient group with a distinct biomarker pattern
Endotype also known as biotype	Subphenotype with a unique underlying biological/molecular mechanism
Exotype	Endotype that is conserved across disease states, syndromes or phenotypes
Treatable trait	Endotype that can be targeted using a specific therapy affecting the underlying biological mechanism
Genotype	Patient group with a distinct underlying genetic pattern
Subclass or subtype	Generic term for a subgroup identified using clustering methodology

Although these proposed definitions are distinguished conceptually here, in practice, they may sometimes overlap.

will rarely provide robust risk stratification when compared to traditional statistical methods.[20] A distinction must be drawn between using outcomes to demonstrate clinically important differences between phenotypes (which is reasonable) and using clustering methods as a primary method for risk stratification (which is less effective than many alternative methods).

SUBPHENOTYPING TO DEFINE UNDERLYING PATHOPHYSIOLOGICAL MECHANISMS. An important use of subphenotyping is to identify the underlying pathophysiological processes driving specific disease manifestations. With biomarker testing and an array of "-omics" approaches, deeper insights into individual disease mechanisms may be garnered. Many of the requisite tests are costly and time-consuming, limiting the translation to clinical practice outside of the research setting. Subphenotyping based on readily available surrogate biomarkers that correlate with the underlying disease-specific biomarker(s) of interest could alleviate the need for more extensive testing. Routine clinical data may not reliably correlate with a single underlying disease mechanism to the extent that the specific biomarker patterns and treatment response can be identified. Identifying subphenotypes in real time using a combination of routine clinical data and rapid point-of-care biomarker panels will be necessary for practical implementation. We require a better understanding of the stability of subphenotypes over time, the influence of interventions on the transition between subphenotypes, and the prognosis associated with changes in subphenotypes. An important unanswered question is whether subphenotypes represent clinical states with distinct underlying disease mechanisms vs different manifestations of the same clinical state over time, and it remains possible that progression along a single shared pathophysiological pathway could create the appearance of distinct subphenotypes.

IDENTIFICATION OF TREATABLE TRAITS. The ultimate goal of subphenotyping is to tailor specific treatments to each patient that have the best chance of improving clinical outcomes by identifying treatable traits that allow individualized treatment. If conserved subphenotypes can be identified within CS populations and linked to underlying disease mechanisms that influence treatment responses, then it may be possible to identify treatable traits that can guide clinical care. For example, dipeptidyl peptidase-3 (DPP-3) is a cardiodepressant biomarker that is elevated in patients with severe or refractory CS.[78,79] If elevated DPP-3 levels characterize a unique CS subphenotype and a DPP-3 inhibitor was clinically available, then this might define a treatable trait.[79] Importantly, if a certain intervention was only effective in one subphenotype of CS patients that was underrepresented in an RCT population, then the study would fail to show an overall benefit even though a segment of the population responded favorably.[71,80] To date, secondary analyses from RCTs in CS populations have not consistently identified subgroups with clear differential treatment effects, yet these subgroups were defined using standard clinical variables as opposed to mechanistic subphenotypes.[5,6] As with SCAI Shock stage, it will be ideal to assign subphenotypes a priori during enrollment in future studies to allow stratified randomization and prespecified subgroup analyses.

CONCLUSIONS

In part 1 of this 2-part series, we have emphasized the heterogeneity that exists within the CS population and the challenges that this poses for clinicians and researchers. We have highlighted the development and refinement of the SCAI Shock Classification, examined its clinical and research applications, and identified areas of remaining uncertainty and future evolution. We have detailed the rationale for staging and subphenotyping within the CS population as an approach to develop individualized treatment strategies. In part 2, we will guide the reader through an in-depth discussion of using unsupervised machine learning algorithms to perform subphenotyping and discuss how these methods have been applied to patients with cardiovascular disease and critical illness, including CS.[20]

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Mr Kennedy is supported by NIH/NIGMS 2R35GM119519-06 and NIH/NIGMS 1R21GM144851-01. Dr Baran is a current consultant for Livanova and Getinge; has been a prior consultant for Abiomed and Abbott; is currently on the steering committee of Procyrion and CareDx; and is a speaker (current) for Pfizer. Dr Kapur has received speaker honoraria/consultant fees from Abbott, Abiomed, Boston Scientific, Edwards, Getinge, LivaNova, and Zoll; and has received institutional research grants from Abbott, Abiomed, Boston Scientific, Getinge, and LivaNova. Dr Mebazza has received personal fees from Orion, Roche, Adrenomed, and Fire 1; and grants and personal fees from 4TEEN4, Abbott, Roche, and Sphyngotec. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS **cardiac intensive care unit, cardiogenic shock, mortality, phenotypes, shock**